

31 PRTS

10/551038

JC09 Rec'd PCT/PTO 27 SEP 2005

- 1/12 -

DESCRIPTION

PRODUCTION METHOD OF MATERIALS FOR CANCER TREATMENT

5 TECHNICAL FIELD

[0001]

The present invention relates to a method of producing a material for cancer treatment to be used for cancer treatment such as radiation therapy and thermotherapy.

10

BACKGROUND ART

[0002]

[Patent Document 1] JP06-62439, B

[Patent Document 2] JP02-119784, A

15 [Patent Document 3] JP2000-258596, A

[Non-Patent Literature Document 1] Chemical Industry, Vol.52, No.5 (2001) 38-43

[Non-Patent Literature Document 2] Journal of Chemical Engineering of Japan, Vol.26, No.2 (1993) 223-224

20 [Non-Patent Literature Document 3] New Ceramics, (1993) No.1, 47-50

[Non-Patent Literature Document 4] Annual Meeting of The Ceramic Society of Japan (2001) 270

[Non-Patent Literature Document 5] "Preparation of magnetite microspheres for hyperthermia of cancer," pp. 645-648 in

25 Bioceramics Vol. 14, Ed. by S. Brown, I. Clarke and P. Williams, Trans Tech Publications Ltd., Switzerland, 2001

[0003]

Since the medical treatment method carried out by sending microspheres made of a radioactive material to a diseased part by a

catheter via a blood vessel and directly radiating radioactive beam to a cancer is capable of radiating a sufficient dose of radioactive beam to the diseased part without damaging the normal tissues in the vicinity of the body surface as compared with radiation therapy by radiating radioactive beam from the outside, its application is highly expected. Also, since a medical treatment method carried out by sending microspheres made of a ferromagnetic material to a diseased part by a catheter via a blood vessel and locally heating the diseased part by setting the diseased part in an alternating magnetic field is capable of heating the diseased part deep in vivo without damaging the normal tissues as compared with treatment by heating from the outside of the living body, the application is expected.

As the above-mentioned radioactive material, an yttria-containing glass (Patent Document No. 1) and a crystalline yttria (Patent Document No. 2) produced by high frequency induced thermal plasma method are proposed. Also, as the ferromagnetic material, magnetite-containing glass-ceramics and a magnetite crystal produced by high frequency induced thermal plasma method (both non-Patent Literature Document No. 1), and a magnetite crystal precipitated from an aqueous solution (non-Patent Literature Document No. 5) are proposed.

DISCLOSURE OF THE INVENTION

[0004]

However, the above-mentioned materials have high specific gravity values and clog a catheter and thus are hard to send prescribed amount of microspheres to a diseased part. Further, the sent microspheres descend in a body of a patient owing to the

self-weight without staying in the diseased part and their distribution becomes uneven.

Therefore, an object of the invention is to provide a material for cancer treatment easy to be transported by means of a catheter and prone to stay in a diseased part.

[0005]

To achieve the object, the method for the production of the material of the invention comprises preparing a first aqueous solution and a second aqueous solution; obtaining a precipitate by adding the second aqueous solution to the first aqueous solution; and drying the obtained precipitate.

The first aqueous solution is obtained by dissolving a metal becoming insoluble in an alkaline solution and a carboxylic acid amide under acidic or neutral condition.

The second aqueous solution is obtained by dissolving an enzyme catalyzing hydrolysis of the carboxylic acid amide and an organic polymer becoming gel by reaction with a component of the first aqueous solution or energy application from the outside.

[0006]

Hereinafter, the case that the organic polymer becomes gel by reaction with the component of the first aqueous solution and the case that the organic polymer becomes gel by energy application from the outside will be described separately. In the case of the former, when the second aqueous solution is added to the first aqueous solution, the second aqueous solution takes the first aqueous solution therein to be gel. In the case the second aqueous solution to be added is in droplet state, gelation occurs in granular form. The carboxylic acid amide held in the gel is hydrolyzed by the function of the enzyme and the produced hydroxide

ion increases the pH of the first aqueous solution. Then, the metal ionized and dissolved in the first aqueous solution is bonded with the hydroxide ion to form a precipitate. Since the above-mentioned enzyme is fixed in gel (particles), the hydrolysis is promoted only in the inside of the gel (particles) and in the vicinity of the gel (particles) to produce a precipitate reflecting the shape of the gel (particles). Since the gel (particles) is porous, the precipitate becomes porous and thus its specific gravity is small.

[0007]

If the above-mentioned metal is yttrium, yttria particles having radioactive property can be produced and if iron, magnetite (Fe_3O_4) or maghemite ($\gamma\text{-Fe}_2\text{O}_3$) particle showing magnetic property can be produced. Besides, zinc, magnesium, and manganese may be contained.

If the metal is derived from a nitric acid salt, the salt is easy to be dissolved in the first aqueous solution and therefore it is preferable. The carboxylic acid amide is defined in a broad definition including urea and may include all those which are defined by the general formula RCONH_2 . In the formula, R is not particularly limited and may be residual groups formed by removing the carboxyl group from carboxylic acid and besides, an amino group. In the case R is amino, it becomes urea.

[0008]

Preferable as the above-mentioned organic polymer are an alginic acid salt and an alkyl cellulose derivative salt, because they carry out gelation by reaction with iron ion and yttrium ion, respectively.

Next, the case of carrying out gelation by energy application will be described. If the organic polymer is an albumin, gelation

takes place by moderate heating and if an agar or a gelatin, gelation takes place by cooling. In the case gelation of the organic polymer is caused by the energy application from the outside, it is preferable to add the organic polymer to the first aqueous solution after previous generation by the method. Further, if the organic polymer is a pectic acid, gelation is carried out by reaction with saccharides and if a carrageenan, gelation is carried out by reaction with potassium ion under cooling condition. In these cases, the saccharides or potassium ion may be added previously in the first aqueous solution. The saccharides can be removed by firing after the precipitate is produced.

The crystallization of the precipitate is promoted and chemical durability is increased by firing the precipitate after drying and therefore, it is preferable.

[0009]

Means for adding droplets of the second aqueous solution to the first aqueous solution may include dropwise addition by a dropping pipe, spraying, and also a vibration orifice method. The vibration orifice method is for jetting the second aqueous solution from an orifice with a hole diameter about several tens μm by ultrasonic vibration. According to the method, the particle diameter of the droplets can be determined based on the following expression and it is made possible to produce very small droplets with an even particle size by controlling the vibration frequency and the concentration of the second aqueous solution.

$$d = \{(6QC) / (\pi f)\}^{1/3}$$

d: particle diameter,

Q: flow speed of solution (jetting speed)

C: concentration by volume of solute in solution

f: vibration frequency (Hz)

[Effects of the invention]

[0010]

5 As described, according to the invention, particles with a low specific gravity and having efficacious properties such as radiation and magnetic properties for medical treatment of cancer can be produced and the particles are easy to be transported by a catheter and prone to stay in a living body and thus useful for
10 medical treatment of cancer.

BRIEF DESCRIPTION OF THE DRAWINGS

[0011]

15 Fig. 1 is SEM photographs showing gel particle (after firing) of Example 1.

Fig. 2 is SEM photographs showing gel particle (after drying) of Example 2.

Fig. 3 is a SEM photograph showing gel particle (after firing) of Example 2.

20

BEST MODE FOR CARRYING OUT THE INVENTION

[0012]

Example 1

25 A first aqueous solution was prepared by adding 0.75 g of urea to 300 mL of 0.1 M yttrium nitrate (n) hydrate $Y(NO_3)_3 \cdot nH_2O$ and 10 mL of a second aqueous solution containing 1 mg of urease (derived from rapeseed) and 330 mg of carboxymethyl cellulose sodium salt was prepared.

Ten milliliters of the second aqueous solution was dropwise

added by a dropping pipe to 300 mL of the first aqueous solution. Immediately after dropwise addition, the droplets independently became gel. The resulting product was left at 36 °C for 4 days and gel particles were washed successively with water and ethanol and then freeze-dried. Then, the dried gel particles were heated at 5 °C/minute and fired by keeping them at respective temperatures in a range of 600 to 1300 °C for 2 hours. The diameter of the dried gel particles was about 2 to 3 mm and it became 0.5 to 1 mm after firing. [0013]

The gel particles after firing were analyzed by a powder x-ray diffractometer to find only peaks for cubic yttrium oxide. The scanning electron microscopic (SEM) photographs of gel particles fired at 1100 °C are shown in Fig. 1. In Fig. 1, the photographs in the upper group show the outer appearance and the photographs in the lower group show a cross sectional view and the photographs in the right side in the respective groups are magnified portions of the photographs in the left side. As shown in the photographs, although no pore was formed in the surfaces of the gel particles, the insides were just like a honeycomb. That was in common among all of the gel particles fired at temperatures in a range of 600 to 1200 °C. Only the gel particles fired at 1300 °C were found having broken surfaces.

When the gel particles fired at 1000 °C were dropped in water in a beaker, it took them 3 seconds to reach the bottom in 10 cm depth from the water surface.

[0014]

Example 2

A first aqueous solution containing 0.1 M iron nitrate nonahydrate $\text{Fe}(\text{NO}_3)_3 \cdot 9\text{H}_2\text{O}$ and 0.041 M urea, and 10 mL of a second

aqueous solution containing 1.0 mg of urease (same as used for Example 1) and 3% by weight of ammonium alginate were prepared.

Ten milliliters of the second aqueous solution was dropwise added by a dropping pipe to 150 mL of the first aqueous solution. Immediately after dropwise addition, the droplets independently became gel. The resulting product was left at 36 °C for 3 days and gel particles were washed successively with water and ethanol and then freeze-dried. Then, the dried gel particles were heated at 5 °C/minute and fired by keeping them at 400 °C for 3 hours in 70CO₂+30H₂ mixed gas atmosphere. The diameter of the dried gel particles was about 1.5 mm and it became about 0.5 mm after firing.

The gel particles after firing were analyzed by a powder x-ray diffractometer to find only peaks for maghemite. The SEM photographs of the gel particles after drying are shown in Fig. 2. In Fig. 2, the photographs in the upper group show the outer appearance of gel particles and the photographs in the lower group show the outer appearance of other gel particles divided into two parts and having round shapes at the time of drying and the photographs in the right side in the respective groups are magnified portions of the photographs in the left side. Also, a SEM photograph of the gel particles after firing is shown in Fig. 3. As shown in the photographs, although no pore was formed in the outer surfaces of the gel particles, the insides were hollow.

When the fired gel particles were dropped in water in a beaker, it took them 3 seconds to reach the bottom in 10 cm depth from the water surface.

[0015]

Comparative Example

A fine powder containing 99.9% by weight of yttria was melted

by high frequency thermal plasma under the following conditions and made spherical.

Carrier gas for powder supply: Ar 5L/min

Plasma gas composition: Ar 90 L/min + O₂ 5 L/min

5 High frequency oscillator: plate input 40 kW, frequency 4 MHz

The spherical particles were dispersed in ultra pure water with a specific resistance 18 MΩ · cm and sieved by using a nylon sieve. Microspheres of 20 to 30 μm in diameter and containing more than 99% by weight of Y₂O₃ were obtained. When the resulting
10 microspheres were dropped in water in a beaker, it took them 1 second to reach the bottom in 10 cm depth from the water surface.